WHO HANDBOOK FOR REPORTING RESULTS OF CANCER TREATMENT

WORLD HEALTH ORGANIZATION

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1. INTRODUCTION

During the last few decades there has been a rapid and continuous increase in the number of investigations of cancer therapy carried out in many parts of the world. This has resulted in an enormous expansion of the cancer literature. However, these investigations are frequently reported in a way which makes it difficult for investigators to compare their results with those of others: essential details of the therapy may be missing, and the methods of evaluating the data can vary considerably. Therefore it has become necessary to develop a "common language" to describe cancer treatment and to agree on internationally acceptable general principles for evaluating data.

On the initiative of the World Health Organization two meetings on the standardization of reporting results of cancer treatment were held - in Turin in 1977, and in Brussels in 1979 - with representatives of the European Organization for Research on Treatment of Cancer (EORTC), the National Cancer Institute of the USA, the International Union Against Cancer (UICC), and the Council for Mutual Economic Assistance (CMEA), as well as with members of several other organizations. This handbook is the result of these combined efforts.

2. BASELINE DATA

Minimum sets of data on the characteristics of patients and tumours are necessary for identification of a patient population under treatment. This allows for a more complete evaluation of the reported data and results. A number of the recommendations in the WHO Handbook for Standardized Cancer Registries (Hospital-based) (1) are useful for this purpose.

2.1 DATA RELATING TO THE PATIENT

2.1.1 Minimum data

It is recommended that the minimum data should include:

1. Name of the patient.
2. Address.
3. Hospital number or other identification number.
4. Sex.
5. Year of birth (estimated, if necessary).
6. Place of birth.
7. Height and weight.
8. Relevant medical history and all prior antitumour therapy.

9. Performance status; a 5-grade scale is recommended:

Grade	Performance status
0	Able to carry out all normal activity without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out light work.
2	Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours.
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

2.1.2 Additional data

Often in clinical trials, and in cancer therapy in general, it is helpful to obtain additional data relating to the patient:

1. Nutritional status.
2. Specific habits.
3. Socioeconomic status.

It is recommended that these and similar factors which may influence the behaviour of the neoplasm and/or the antitumour therapy should be specified when indicated.

2.2 DATA RELATING TO THE TUMOUR

The minimum data set desirable is as follows:

1. Site of the primary tumour. ICD-O is recommended for topography coding (2).

2. Mention should be made of whether the tumour or lesions are measurable - bidimensionally or unidimensionally - or unmeasurable.

3. Measure the size of the tumour or the lesions used to evaluate the result of the therapy. Give, in centimetres, the maximum diameter(s) and second transverse diameter(s), at a right angle to the first and in the same plane. For liver measurement see 5.1.1.2.

4. Histopathology with recording of tumour type, grade and stage. Use of the ICD-O morphology codes is recommended.

5. Anatomical extent of the disease.

6. Clinical stage should be recorded before the start of therapy. It is recommended that the UICC TNM system be used whenever applicable (3). Where surgery has been used to complete the staging, the extent of the disease, what was examined, what was found, and the resulting surgicopathological stage should also be recorded.

2.3 LABORATORY AND RADIOLOGICAL DATA

1. Complete blood count.

2. Renal and liver function tests.

3. Pertinent radiological assessment.

4. Tumour markers can be important, such as:
   - gonadotrophins for trophoblastic tumours,
   - fetoprotein for liver tumours,
   - globulins for myelomas.

5. When possible, an attempt should be made to determine tumour doubling time.

6. Evaluation of immune status, if done.

7. Special investigations to delineate further the extent of the disease may be helpful for several tumours.

3. REPORTING OF TREATMENT

Since the treatment methods should be reproducible, it is necessary to report sufficient information to interpret and evaluate the therapy used. It is important to indicate whether the specific therapy, be it a single mode or a combined modality, is used to induce an antitumour effect or to maintain a condition.

It should be emphasized that in this document the term "adjuvant therapy" is not used. What can be considered as adjuvant to primary therapy today may become primary tomorrow. It is therefore recommended that the term "combined modality therapy" be used when more than one form of treatment is used.

3.1 SURGERY

3.1.1 Description of the operation

A precise description of the surgical procedures must be given, subdivided in the following categories:

(a) Local excision of the tumour without excision of regional lymph nodes.

(b) Local excision of the tumour with excision of the regional lymph nodes.

(c) Excision of the tumour with the involved organ, without excision of the regional lymph nodes.

(d) Excision of the tumour with the involved organ, with excision of the regional lymph nodes.

(e) Excision of the tumour extended to adjacent organs. (This can include removal of the involved organ where applicable.)

(f) Partial excision of the tumour (reduction, debulking or other).

(g) Excision of metastatic lesions.

(h) Reconstructive surgery.

(i) Surgery for alleviation of symptoms only.

(j) Other surgery (i.e., exploratory, second look).

3.1.2 Whenever relevant, it is recommended that the surgeon should state at the end of the operation whether the procedure is potentially curative or not.

3.1.3 Major complications following surgery should be described.

3.2 RADIOTHERAPY

The following minimum specifications and descriptions are recommended:

3.2.1 Treatment plan.

3.2.2 Methodology, etc.

(a) Source of radiation (e.g., isotope, treatment machine).

(b) Type of radiation (e.g., photon, neutron).

(c) Energy of radiation.

(d) Method of application (e.g., external beam interstitial).

(e) Sites treated, including field sizes.

(f) Dosage-time relationship, specifying:

1. Total dose,

2. Individual doses,

3. Dose rate,

4. Fractionation scheme,

5. Overall time.

3.2.3 Radiosensitizers or protectors should be described when used.

3.2.4 Indication of whether the intent was:

(a) Curative,

(b) Palliative.

3.2.5 When treatment is not completed, the reason(s) for this should be specified.

3.2.6 Complications (see section 4)

3.3 CHEMOTHERAPY, INCLUDING HORMONAL THERAPY

A precise description should be given of:

3.3.1 Treatment plan.

3.3.2 Drugs.

Description of drug administration should include:

1. Drug name - use of nonproprietary name is recommended.

2. Routes and duration of administration.

3. Dosages - specify per kg of body weight or body surface in square metres and amount (e.g., mg, g).

4. Schedule and duration.

5. Specify whether the drugs used are given singly, concurrently or in sequence.

3.3.3 Proportion of the planned doses, courses and cycles actually given, if possible.

3.3.4 Reasons for dosage modifications or delays in drug administration.

3.3.5 Complications (see section 4).

3.4 IMMUNOTHERAPY

A precise description should be given of:

1. Agents or materials used.
2. Sources and strains.
3. Routes and duration of administration.
4. Dosage.
5. Frequency of the administration.
6. Complications (see section 4).

3.5 OTHER THERAPY

A precise description should be given.

3.6 COMBINED MODALITY THERAPY

Each of the modalities should be described individually as under sections 3.1 - 3.5.

The time-relationship of the different forms of therapy should be clearly specified - e.g., whether given concurrently, sequentially, during primary therapy or maintenance therapy, or other.

4. TOXIC EFFECTS

The management of malignancies frequently requires the use of treatment modalities which are associated with significant toxic effects. The acceptability of specific therapy can be assessed by comparing its benefits with its potential cost in terms of toxicity. For this reason the documentation of toxicity is a crucial part of reporting treatment results. For purposes of classification, toxic effects are best divided into acute plus subacute, and chronic or late, rather than in terms of specific treatment modalities.

4.1 ACUTE AND SUBACUTE TOXIC EFFECTS

Grading of acute and subacute toxic effects has several important advantages:

1. It permits comparison of toxicity between treatment programmes.
2. It permits computerized storage and analysis of such toxicity data.
3. It allows uniform treatment modification within a therapeutic programme.

The attachment of clinical significance (e.g., mild, moderate, severe, life-threatening) to a grade should be avoided. A 5-grade system is recommended for general use: grades 0 - 4. No attempt has been made to be all-inclusive and investigators will undoubtedly need to add some toxic manifestations (see Table 1).

4.2 DEATH DUE TO TREATMENT

Several forms of cancer treatment can result in or contribute to death. Such deaths must be reported separately.

4.3 CHRONIC AND LATE TOXIC EFFECTS

Chronic and late toxic effects are becoming more common as more effective treatments result in longer survivals. The severity of these manifestations is less easily quantified than that of acute effects. It is suggested that the following format should be used in reporting these toxic effects:

1. Organ site or system affected.
2. Timing in relation to presumed causative therapy.
3. Nature of toxicity or disability (include second malignancy).
4. Magnitude of symptoms.
5. Impact on performance status (see section 2.1.1).
6. Therapy required.
7. Response to therapy.

It is recommended that patients should be evaluated annually for chronic and late toxicity.

TABLE 1 RECOMMENDATIONS FOR GRADING

	Grade 0	Grade 1
Haematological (Adults)		
Haemoglobin	≥ 11.0g/100ml ≥ 110 g/l ≥ 6.8 mmol/l	9.5 - 10.9g/100ml 95 - 109 g/l 5.6 - 6.7 mmol/l
Leukocytes ($1000/mm^3$)	≥ 4.0	3.0 - 3.9
Granulocytes ($1000/mm^3$)	≥ 2.0	1.5 - 1.9
Platelets ($1000/mm^3$)	> 100	75 - 99
Haemorrhage	None	Petechiae
Gastrointestinal		
Bilirubin	≤ 1.25 x N[a]	1.26 - 2.5 x N[a]
Transaminases (SGOT/SGPT)	≤ 1.25 x N[a]	1.26 - 2.5 x N[a]
Alkaline phosphatase	≤ 1.25 x N[a]	1.26 - 2.5 x N[a]
Oral	No change	Soreness/ erytherma
Nausea/vomiting	None	Nausea
Diarrhoea	None	Transient, < 2 days
Renal		
Blood urea nitrogen or Blood urea creatinine	≤ 1.25 x N[a]	1.26 - 2.5 x N[a]
Proteinuria	No change	1+ <0.3 g% <3 g/l
Haematuria	No change	Microscopic

OF ACUTE AND SUBACUTE TOXIC EFFECTS

Grade 2	Grade 3	Grade 4
8.0 - 9.4g/100ml 80 - 94 g/l 4.95 - 5.8 mmol/l	6.5 - 7.9g/100ml 65 - 79 g/l 4.0 - 4.9 mmol/l	<6.5g/100ml <65 g/l <4.0 mmol/l
2.0 - 2.9	1.0 - 1.9	1.0
1.0 - 1.4	0.5 - 0.9	<0.5
50 - 74	25 - 49	<25
Mild blood loss	Gross blood loss	Debilitating blood loss
2.6 - 5 x N^a	5.1 - 10 x N^a	>10 x N^a
2.6 - 5 x N^a	5.1 - 10 x N^a	>10 x N^a
2.6 - 5 x N^a	5.1 - 10 x N^a	>10 x N^a
Erythema, ulcers; can eat solids	Ulcers; requires liquid diet only	Alimentation not possible
Transient vomiting	Vomiting requiring therapy	Intractable vomiting
Tolerable, but > 2 days	Intolerable, requiring therapy	Haemorrhagic dehydration
2.6 - 5 x N^a	5 - 10 x N^a	>10 x N^a
2 - 3+ 0.3 - 1.0 g% <3 - 10 g/l	4+ >1.0 g% >10 g/l	Nephrotic syndrome
Gross	Gross + clots	Obstructive uropathy

TABLE 1 RECOMMENDATIONS FOR GRADING

	Grade 0	Grade 1
Pulmonary	No change	Mild symptoms
Fever with drug	None	Fever $< 38\ ^{o}C$
Allergic	No change	Oedema
Cutaneous	No change	Erythema
Hair	No change	Minimal hair loss
Infection (specify site)	None	Minor infection
Cardiac		
Rhythm	No change	Sinus tachycardia, >110 at rest
Function	No change	Asymptomatic, but abnormal cardiac sign
Pericarditis	No change	Asymptomatic effusion

OF ACUTE AND SUBACUTE TOXIC EFFECTS (continued)

Grade 2	Grade 3	Grade 4
Exertional dyspnoea	Dyspnoea at rest	Complete bed rest required
Fever 38 °C - 40 °C	Fever >40 °C	Fever with hypotension
Bronchospasm; no parenteral therapy needed	Bronchospasm; parenteral therapy required	Anaphylaxis
Dry desquamation, vesiculation, pruritus	Moist desquamation, ulceration	Exfoliative dermatitis; necrosis requiring surgical intervention
Moderate, patchy alopecia	Complete alopecia, but reversible	Non-reversible alopecia
Moderate infection	Major infection	Major infection with hypotension
Unifocal PVC, artrial arrhythmia	Multifocal PVC	Ventricular tachycardia
Transient symptomatic dysfunction; no therapy required	Symptomatic dysfunction responsive to therapy	Symptomatic dysfunction non-responsive to therapy
Symptomatic; no tap required	Tamponade; tap required	Tamponade; surgery required

TABLE 1 RECOMMENDATIONS FOR GRADING

	Grade 0	Grade 1
Neurotoxicity		
State of consciousness	Alert	Transient lethargy
Peripheral	None	Paraesthesias and/or decreased tendon reflexes
Constipation[b]	None	Mild
Pain[c]	None	Mild

[a] N = upper limit of normal value of population under study.

[b] This does not include constipation resultant from narcotics.

[c] Only treatment-related pain is considered, not disease-related depending upon the tolerance level of the patient.

OF ACUTE AND SUBACUTE TOXIC EFFECTS (concluded)

Grade 2	Grade 3	Grade 4
Somnolence <50% of waking hours	Somnolence >50% of waking hours	Coma
Severe paraesthesias and/or mild weakness	Intolerable paraesthesias and/or marked motor loss	Paralysis
Moderate	Abdominal distention	Distention and vomiting
Moderate	Severe	Intractable

›ain. The use of narcotics may be helpful in grading pain,

5. REPORTING OF RESPONSE

The guidelines proposed by the Treatment Committee of the Breast Cancer Task Force in the USA (4), and the guidelines proposed for breast cancer as the outcome of a UICC project (5) have served in large measure as the basis for the criteria of response recommended here.

In the past some groups and investigators have reported decreases of less than 50% in tumour size as responses, but it is often not possible to determine this with precision (6). It is recommended that only complete or partial responses as defined below should be used. This will reduce the variability between the results reported by different investigators.

While it is recognized that in some treatment trials shorter durations of response may be useful, in general 4 weeks should be used as the minimum duration of reported response.

Objective response can be determined clinically, radiologically, biochemically or by surgicopathological staging. The method of determining response should therefore always be specified.

The use of a 25% increase in one or more measurable lesions or appearance of a new lesion is recommended for defining progression of disease. This percentage should not necessarily be regarded as influencing the management of the patient.

5.1 MEASURABILITY

5.1.1 Measurable disease

All measurements should be recorded in metric notation, using a ruler or calipers.

5.1.1.1 Bidimensionally measurable

(a) Surface area approximation - multiply the longest diameter by the greatest perpendicular diameter.

(b) Multiple lesions for a single organ site - sum the products of the diameters of all measured lesions.

5.1.1.2 Unidimensionally measurable

(a) Liver enlargement due to tumour involvement - sum the three distances of the inferior liver edge from the xiphoid notch and the right and left costal margins in the respective midclavicular lines.

(b) Other lesions where only one dimension is measurable - record that single dimension.

5.1.2 Unmeasurable disease

There are many forms of unmeasurable disease, and only a few are mentioned as examples:

Lymphangitic pulmonary metastases.

Skin involvement in breast cancer (documented by photograph when possible).

Abdominal masses that can be palpated but not measured.

5.2 DEFINITIONS OF OBJECTIVE RESPONSE

5.2.1 Measurable disease

1. Complete response (CR). The disappearance of all known disease, determined by 2 observations not less than 4 weeks apart.

2. Partial response (PR). 50% or more decrease in total tumour size of the lesions which have been measured to determine the effect of therapy by 2 observations not less than 4 weeks apart. In addition there can be no appearance of new lesions or progression of any lesion.

3. No change (NC). A 50% decrease in total tumour size cannot be established nor has a 25% increase in the size of one or more measurable lesions been demonstrated.

4. Progressive disease (PD). A 25% or more increase in the size of one or more measurable lesions, or the appearance of new lesions.

5.2.2 Unmeasurable disease

1. Complete response (CR). Complete disappearance of all known disease for at least 4 weeks.

2. Partial response (PR). Estimated decrease in tumour size of 50% or more for at least 4 weeks.

3. No change (NC). No significant change for at least 4 weeks. This includes stable disease, estimated decrease of less than 50%, and lesions with estimated increase of less than 25%.

4. Progressive disease (PD). Appearance of any new lesion not previously identified or estimated increase of 25% or more in existent lesions.

5.2.3 Bone metastases

A separate set of response criteria is necessary for bone metastases:

1. Complete response (CR). Complete disappearance of all lesions on X-ray or scan for at least 4 weeks.

2. Partial response (PR). Partial decrease in size of lytic lesions, recalcification of lytic lesions, or decreased density of blastic lesions for at least 4 weeks.

3. No change (NC). Because of the slow response of bone lesions the designation "no change" should not be applied until at least 8 weeks have passed from start of therapy.

4. Progressive disease (PD). Increase in size of existent lesions or appearance of new lesions.

Note: Occurrence of bone compression or fracture and its healing should not be used as the sole indicator for evaluation of therapy.

5.3 DETERMINATION OF OVERALL RESPONSE IN SOLID TUMOURS

5.3.1 If both measurable and unmeasurable disease is present in a given patient, the result of each should be recorded separately. Note that an overall assessment of response involves all parameters.

5.3.2 In patients with measurable disease, the poorest response designation shall prevail.

5.3.3 "No change" in unmeasurable lesions will not detract from a partial response in measurable lesions but will reduce a complete response in measurable lesions to partial response overall.

5.3.4 If in the totals of responses by organ site there are equal or greater numbers of complete plus partial responses than of "no change" designations, then the overall response will be partial.

5.3.5 If progressive disease exists in any lesion or when a new lesion appears, then the overall result will be "progressive disease".

5.4 DURATION OF RESPONSE

1. The period of complete response lasts from the date the complete response was first recorded to the date thereafter on which progressive disease is first noted.

2. In those patients who only achieve a partial response, only the period of overall response should be recorded.

3. The period of overall response lasts from the first day of treatment to the date of first observation of progressive disease.

5.5 SUBJECTIVE RESPONSE

Definition of subjective response is difficult because so many factors can influence it. Despite this difficulty, a positive response (e.g., weight gain or decrease in pain) can nevertheless be of great importance to the patient and may alert the physician to the possibility of an objective response. In general, the performance status of patients and their weights are the most reliable parameters.

5.5.1 Performance status (see 2.1.1)

Performance status should be recorded before, at regular intervals during the treatment, and at the end. A consistently improving performance status can be regarded as response, while a decrease can be indicative of progressive disease.

5.5.2 Weight

Patients' weight should be recorded regularly.

5.6 REVIEW

Independent review of response and of its duration is recommended.

6. REPORTING OF RECURRENCE AND DISEASE-FREE INTERVAL

For the purpose of simplicity, the word "recurrence" is here used to indicate reappearance of disease. "Relapse" can also be used, and "progression of disease" may be used where appropriate.

While the interval between treatment and death is a major measure of effectiveness of therapy, one of the important benefits of therapy is the prolongation of the interval between treatment and recurrence, which may or may not be accompanied by improvement in survival. It is therefore necessary to define recurrence and the interval from treatment to recurrence for each treatment.

In order to define the time of recurrence as accurately as possible, the frequency of examination and duration of follow-up should be specified. Time to recurrence or death should be measured from the first day of therapy.

6.1 DIAGNOSIS OF RECURRENCE

One or more of the following must be positive - and should be recorded - for a diagnosis of recurrent disease to be acceptable:

1. Histology or cytology.
2. Reappearance of old lesion(s) or appearance or new lesion(s).
3. Response to specific therapy of lesion(s) considered suspicious only.
4. Postmortem examination.

6.2 CLASSIFICATION OF RECURRENCE

Lesions can be categorized broadly as loco-regional or distant. A precise description of the

sites of recurrence or metastasis should be given. Where radiotherapy has been employed, a distinction should be made between whether disease has or has not reappeared within the irradiated volume.

6.3 DATE OF FIRST RECURRENCE

This should be based on the onset of a sign. The date of first detection of a palpable lesion is acceptable only when the diagnosis of tumour involvement is subsequently established. The diagnosis of recurrent disease by X-rays or scans should be dated from the first positive record, even if determined in retrospect. Disease-specific markers and disease-specific symptoms may be used to backdate the time of recurrence.

6.4 RECORDING AND REVIEW

All dates should be recorded by those responsible for the care of the patient. Dates of first recurrence, metastasis, and death should be confirmed by an independent reviewer whenever possible. Data based on suspicion alone should be verified in order to establish their accuracy. In addition, the case records of patients not reported as having recurrent disease should be scrutinized annually.

6.5 CLASSIFICATION OF CASES

A. Alive, without recurrence.

B. Alive, with recurrence.

C. Alive, recurrence unknown.

D. Dead, without recurrence.

E. Dead, with recurrence.

F. Dead, recurrence unknown.

G. Lost, without recurrence.

H. Lost, with recurrence.

I. Lost, recurrence unknown.

6.6 DISEASE-FREE INTERVAL

Following surgery, the term "disease-free interval" (DFI) is recommended for the period during which there is no evidence of disease activity; it is calculated from the day of surgery to the first day of recurrence.

7. DETERMINATION OF RESULTS OF THERAPY

7.1 INTRODUCTION

7.1.1 Completeness of data is the most important factor in considering the result of cancer therapy. Without this, it is impossible to make a valid evaluation of the results and ensure a valid comparison of clinical investigations.

In the reporting of results, a division can be made into two broad categories of measurable quantities:

(a) Frequency: The frequency of an event is usually the first measurement used to evaluate a treatment. It can represent the frequency of recurrences following primary therapy, the proportion of responders, the proportion of survivors, the frequency of treatment failure, and others. In common usage, the term "rate" is often used to describe the frequency of occurrence of events. This is unfortunate as "rate" often implies the number of events occurring during a time interval, for example a year, in a defined population.

(b) Duration: The duration of several factors can be important. Examples are the duration of time to recurrence, duration of response, duration of survival.

Consideration of both frequency and duration will improve the completeness of reports. For instance, following the primary treatment of breast cancer, it is useful to learn not only the frequency of recurrence but also the time to recurrence as well as the survival. On the other hand, when advanced breast cancer is being treated, it is necessary to determine the proportion of responders, the duration of responses,

as well as survival. Thus the appropriate factors or quantities to measure can vary with the disease, the stage of that disease, and the treatment.

7.1.2 Numerators and denominators

In expressions of the results of cancer treatment, the numerator is the number of patients in whom events occur during a given period of observation, and the denominator is the total number of patients at risk during that same period. In many reports authors do not clearly define the numerator or denominator used to report their results. Often a single denominator is used from which many patients in the original population have been deleted for a variety of reasons such as: lost to follow-up, early death, inadequate data, failure to complete therapy due to toxicity, refusal by the patient of further therapy. Such deletions can lead to a falsely high frequency or duration for a group.

7.1.3 Maturity of data

When a large proportion of patients has been followed for a short length of time the reporting of duration may be relatively meaningless. Similarly, the frequency of recurrence may be low and as yet of limited importance. It is important, therefore, to ensure that data have matured long enough to provide precision in the reported results, and the follow-up periods should always be specified. It may be noted that the length of the observation period required will tend to vary with different tumours.

7.1.4 Accuracy of dates

There are many forms of inaccuracy which can distort reported treatment results. A very important one is in the follow-up. If this is infrequent or poor, patients may be considered lost to follow-up

or even alive and healthy when in reality they may be dead. Before reporting results, therefore, every effort should be made to confirm the state of the patient as well as identifying the date on which an event occurs.

7.1.5 The problem of "cure"

The definition of "cure" is difficult and by many considered impossible. One criterion used is a survival experience among a group of patients identical to the survival experience of the general population with the same distribution of demographic factors, i.e., when the relative survival ratio is 1. Another option is to regard a patient as cured when he or she has survived in a disease-free state long enough to enter a group with a known low probability of developing a recurrence. Some prefer the term "recovered" for those patients for whom it is known that there is a low probability of subsequent death from the initial neoplasm.

7.2 PATIENT POPULATION

The patients to be considered in reporting results can be classified as follows:

(a) Patients available for treatment.

(b) Patients considered eligible and registered for a given therapy (criteria for eligibility and ineligibility should be specified).

(c) Patients given therapy.

(d) Patients adequately treated (the definition of adequate should be stated before therapy is started and not at the end of a study).

The patients used to determine the results of therapy are often called "evaluable patients". However, this term is frequently not defined. This

is one of the reasons for which different reports give different efficacies for the same therapy. Therefore, it is necessary to clearly describe those patients not considered evaluable. It may be noted that patients evaluable for toxicity may not necessarily be evaluable for response.

7.3 DENOMINATORS

At least two of the following three denominators are recommended for reporting results:

(a) Registered and eligible. (N.B.: The number of patients registered and entered on study but subsequently found to be ineligible and the reasons for their ineligibility must be reported.)

(b) Registered, eligible, and treated: this includes all patients who were registered, were eligible, and were given therapy regardless of how little or how much therapy was given.

(c) Registered, eligible, and adequately treated.

When other denominators are used, they should be clearly defined.

7.4 CALCULATION OF RESULTS

7.4.1 Relative frequencies and proportions

In the calculation of relative frequencies and proportions only the numerators and denominators are important. The findings can best be presented in the form of a table in which these are clearly identified. It is recommended that the actual numbers should always be given. Table 2 is an example.

TABLE 2

Example of Presentation of Data to Show Response to Cancer Therapy

Denominators		Numerators and percentages							
		Complete response (CR)		Partial response (PR)		No change (NC)		Progressive disease (PD)	
	N	N	%	N	%	N	%	N	%
Registered and eligible	100	30	30	30	30	25	25	15	15
Registered, eligible, and treated	90	30	33	30	33	19	21	11	12
Registered, eligible, and adequately treated	75	29	39	26	35	15	20	5	7

It is possible to combine two numerators. Thus, if in the first line CR and PR were combined, the numerator would be 60 and the proportion 60%. Note also that proportions (percentages) may not add up exactly to 100% when they are rounded off.

7.4.2 Duration

The best method to calculate duration is the life-table method because it takes into account the experience of all patients entered into a study. The method can be used to determine length of survival, duration of response, disease-free interval, and other time intervals.

Investigators not fully acquainted with the methods of calculation are encouraged to enlist the assistance of a statistician.

Whether investigators calculate the life-tables themselves or enlist the assistance of others, it is always necessary to account for all patients. An example of a tabular presentation of the complete data is given in Table 3. The first interval should start with the day the therapy was commenced. When another starting date is used this should be specified.

Table 3

Example of Presentation of Data in a Study of 120 Patients Over 2 Years

	Groups followed during part or all of the interval							
				Died				
Interval (months)	Lost to follow-up	Withdrawn, alive	Alive and followed for part of interval	Without recurrence	Recurrence observed earlier	Recurrence in interval	Alive, developed recurrence	Alive, remained disease-free
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
0–5	3	1	6	1	0	2	2	105
6–11	0	4	5	0	2	1	1	94
12–17	2	7	8	2	1	4	2	69
18–23	1	2	11	3	2	2	2	48

Column 1: The time intervals, here expressed in 6-month periods, can be changed depending on the nature of the disease, type of therapy, etc.

Column 2: The number of patients on whom no information is obtained, despite repeated efforts.

Column 3: Patients withdrawn by the physician (or the patient decides not to continue).

Column 4: Patients who remained in study during only part of the interval.

Column 5: Died with no evidence of disease recurrence.

Column 6: Died with recurrence diagnosed in previous interval.

Column 7: Died with recurrence diagnosed in this interval.

Column 8: Patients who were reported as developing a recurrence during the interval but remained alive throughout.

Column 9: Patients who remained under observation throughout the interval, alive, without disease.

TABLE 4

Example of Life-table Calculation from Data in Table 3 to Determine Disease-free Survival

Interval (months)	Disease-free at beginning of interval	"Withdrawn" during the interval	Recurrence during the interval	At risk of recurrence during the interval	Proportion with recurrence	Proportion remaining disease-free	Disease-free survival
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
0-5	120	11	4	114.5	0.035	0.965	0.965
6-11	105	9	2	100.5	0.020	0.980	0.946
12-17	94	19	6	84.5	0.071	0.929	0.879
18-23	69	17	4	60.5	0.066	0.934	0.821
24-	48						

Column 1: Interval as in Table 3.

Column 2: Derived by subtraction of sum of columns 3 and 4 from column 2 of previous interval. (In this instance the same as column 9 of Table 3 for previous interval.)

Column 3: Sum of columns 2, 3, 4 and 5 in Table 3.

Column 4: Sum of columns 7 and 8 in Table 3.

Column 5: Column 2 less half of column 3. (It is assumed that on average, each patient in column 3 was at risk for half the interval.)

Column 6: Column 4 divided by column 5.

Column 7: 1 minus column 6.

Column 8: Column 7 multiplied by column 8 in the previous interval (e.g., for 6-11-months interval, 0.980 x 0.965 = 0.946).

Note: On occasions it may be necessary to assume that all deaths are due to disease. In this instance, column 5 in Table 3 will be added to column 4 and not column 3 as in this example.

TABLE 5

Example of Life-table Calculation from Data in Table 3 to Determine Overall Survival

Interval (months)	Alive at beginning of interval	"Withdrawn" during the interval	Died during the interval	At risk of death during the interval	Proportion who have died	Proportion who have survived	Overall survival
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
0–5	120	10	3	115	0.026	0.974	0.974
6–11	107	9	1	102.5	0.029	0.971	0.945
12–17	95	17	7	86.5	0.081	0.919	0.869
18–23	71	14	7	64	0.109	0.891	0.774
24–	50						

Column 1: Interval as in Table 3.

Column 2: Derived by subtraction of sum of columns 3 and 4 from column 2 of previous interval.

Column 3: Sum of columns 2, 3 and 4 in Table 3.

Column 4: Sum of columns 5, 6 and 7 in Table 3.

Column 5: Column 2 less half of column 3. (It is assumed that on average, each patient in column 3 was at risk for half the interval.)

Column 6: Column 4 divided by column 5.

Column 7: 1 minus column 6.

Column 8: Column 7 multiplied by column 8 in the previous interval.

Note: If it is certain that deaths without recurrence were not due to disease, then column 5 in Table 3 could be added to column 3 in this example rather than to column 4.

There are several methods of calculating and presenting life-table survival. Tables 4 and 5 provide two examples of life-tables derived from the tabular presentation of the data given in Table 3 to calculate disease-free survival and overall survival.

It is important that investigators should acquire an intuitive feeling about the handling of their own data, but, because of the volume of data and the necessity to examine and report the experience of subgroups identified by specific prognostic factors, analyses are more and more frequently conducted by computer. A method frequently used under such circumstances is that of Kaplan & Meier (7). When this method is used certain data on individuals have to be available - that is, for each patient, the date of start of treatment and the date of events according to the various subdivisions of the data (age, sex, tumour characteristics, etc.) that are being separately considered. Methods are also available to summarize such data for comparisons between groups, such as the log rank method (8). When other methods are used these should be specified.

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Annex

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